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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/611,310	07/01/2003	Ryoichi Hashida	3462.1004-000	3981

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HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
WOODWARD, CHERIE MICHELLE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/611,310	HASHIDA ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 & 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/6/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicant's amendment filed 6 February 2006 is acknowledged. Claims 1-3 and 31 are pending and under examination.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 6 February 2006, per Examiner's request in the Office Action of 4 August 2005, has been considered by the examiner. A signed copy is attached hereto.

Response to Arguments

Claim Rejections Withdrawn

Rejections under 35 USC 103(a)

3. The rejection of claims 1-3 and 31 under 35 U.S.C. 130(a), as being unpatentable over Nakajima et al., (Blood 2001 98(4):1127-1134) is withdrawn in view Applicant's Amendments in Applicants' Response of 6 February 2006. New rejections, necessitated by Amendment, follow.

Claim Rejections Maintained

Rejections under 35 USC 112, First Paragraph, Scope of Enablement

4. The rejection of claims 1-3 and 31 under 35 U.S.C. 112, first paragraph, scope of enablement, for the method of testing all allergic diseases is maintained. Applicant's arguments filed 6 February 2006 have been fully considered but they are not persuasive. Applicant is enabled for diagnosing atopic dermatitis by the recited methods, but not for all allergic diseases. Applicants have not shown how to make and use the invention for all allergic disease.

Applicants' argue that a person of skill in the art could make and use the claimed invention for all allergic diseases without undue experimentation. Applicants' state that the claims have been amended to better define the claimed method. Applicants' state that the amended claims are drawn to a method of testing for an allergic disease by measuring the expression level of a gene or genes encoding TR3, TINUR, or TR3 and TINUR in the eosinophil cells of a test subject. Applicants' argue that the method is a diagnostic, not a therapeutic and that the claims' breadth is limited to a determination of the expression level of just two genes (TR3 and/or TINUR) in one particular cell type (eosinophil cells). Further,

Applicants' argue that the claims are directed to testing for allergic diseases in general and that the specific involvement of eosinophil cells in allergic diseases was well established in the art at the time the application was filed. Thus, Applicants' argue, one having skill in the art would have been able to practice the claimed method based on his knowledge in the art regarding the link of eosinophil cells to all allergic diseases. Without discussing the new matter issues, which are fully explained below, Applicants' arguments have been considered, but are not persuasive.

The specification teaches two genes,"TR3 or TINUR," that are shown to be elevated in eosinophils from patients with atopic dermatitis. It is well-established in the art that eosinophils are involved in hypersensitivity (allergic) immune responses and parasitic infections. Applicants' argue this well-known fact for several pages in their Remarks filed 6 February 2006 (see, i.e. pp. 4-11). TR3 and TINUR are orphan nuclear receptors that have been associated with, for example, various pathologies via the expression of NOT/TINUR and their splice variants in dopaminergic neurons (see i.e. Salin-Nordstrom et al., Society for Neuroscience Abstracts, Society for Neuroscience 1999;25(1/02):p. 1754, abstract 696.3). Although it is well known that eosinophil numbers (i.e. numbers of cells) are generally elevated in hypersensitivity (allergic) disorders, neither the TR3 nor TINUR genes have been shown to be elevated in any cell type in general hypersensitivity reactions. Applicants' have shown TR3 or TINUR genes to be elevated in eosinophils in patients with atopic dermatitis.

At the time the invention was conceived, TINUR and TR3 (as well as NOT, NAK1, Nur77, Nurr1, NGFI-B, and RNR-1) (see specification p. 12) were known to be orphan nuclear receptors that functioned as general coactivators of gene transcription rather than as participants in the induction of specific target genes (Mages *et al.*, *Mol Endocrinol.* 1994 Nov; 8(11):1583-91, previously cited in Office Action of 4 August 2005). There is no disclosure in the specification nor are there any teachings in the art to link the elevation of TR3 or TINUR with general eosinophil activation or degranulation. These two genes are not known to be eosinophil housekeeping genes and they are not known to be associated with any other genes that would be upregulated in a cluster (as with genes that may share a promoter) during eosinophil activation. Applicants have not shown that these two orphan nuclear receptors are elevated whenever eosinophils are generically activated (as in an immune hypersensitivity reaction). Thus, there is no indication in the art or in the specification that TR3 or TINUR would necessarily be elevated in eosinophils in all allergic diseases. Applicants' have not taught how to make or use their invention such that one of ordinary skill in the art would know that TR3 or TINUR were elevated in eosinophils in other allergic diseases. This lack of gene-specific targeting necessitates undue experimentation on the part of the skilled artisan to determine whether these genes are involved in all allergic diseases.

Additionally, Applicants have amended their claims such that they no longer read on measuring TR3 or TINUR gene expression just in eosinophils. Rather, the claims now read on measuring the expression of TR3 or TINUR (or TR3 and TINUR) in a sample, wherein the sample contains eosinophils. A "sample" containing eosinophils reads on a whole blood sample. There are numerous cell types with a whole blood sample, including: monocytes, macrophages, neutrophils, basophils, Tcells, Bcells, eosinophils, NK cells, and various immature myeloid cells, such as dendritic cell precursors. Red blood cells would not be included, as they do not contain a nucleus wherein gene expression could be measured. Applicants have not taught whether the TR3 or TINUR genes are expressed in a cell type other than eosinophils. The claims, as amended, do not provide purification steps such that eosinophils are separated out from the other, potentially contaminating cell types. Thus, a measurement of cDNA by, for example, PCR, from a sample containing a mixed cell population would not provide an accurate or precise measurement of eosinophil gene expression, such that the skilled artisan would be able to discern gene expression in one cell type over another. Applicants' have not taught the expression of TR3 or TINUR in any cell type other than eosinophils in patients with atopic dermatitis.

New Claim Rejections - Necessitated by Amendment

35 USC § 112, First Paragraph, New Matter

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-3 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This is a new matter rejection. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The amendment amending the claim fails to site any support in the specification for the amended subject matter of the amended claim. The claims recite a method of testing for an allergic disease in a test subject, said method comprising the steps of: (a) obtaining a sample from the test subject, said sample containing eosinophil cells; (b) measuring the expression level of a gene or genes encoding the TR3, TINUR, or TR3 and TINUR receptor protein, in the sample; and (c) determining whether the expression level of the gene or genes is elevated compared to the expression level of the gene or genes in eosinophil

cells of normal subjects, wherein a determination that the expression level of the gene or genes in the sample is elevated indicates that the test subject has an allergic disease.

The specification only refers to the TR3 or TINUR genes in the alternative. Measurement of the expression levels of TR3 and TINUR is not described in the specification. The specification fails to describe the correlation that an elevation in TR3 or TINUR indicates that the test subject has an allergic disease. In fact, the specification discloses that an elevation in TR3 or TINUR is indicative of an improvement and a decrease in eosinophils, as in the case of atopic dermatitis (see specification p. 17, lines 35-36 to p. 18, lines 1-3).

Applicants have amended their claims such that they no longer read on measuring TR3 or TINUR gene expression just in eosinophils. Rather, the claims now read on measuring the expression of TR3 or TINUR (or TR3 and TINUR) in a sample, wherein the sample contains eosinophils. A "sample" containing eosinophils reads on a whole blood sample. There are numerous cell types with a whole blood sample, including: monocytes, macrophages, neutrophils, basophils, Tcells, Bcells, eosinophils, NK cells, and various immature myeloid cells, such as dendritic cell precursors. Red blood cells would not be included, as they do not contain a nucleus wherein gene expression could be measured. The specification discusses gene expression of TR3 or TINUR in eosinophil cells, but not expression levels of the gene or genes in samples containing a mixed cell population where the gene expression of other cells will be measured along with that of eosinophils. Applicants have not described whether the TR3 or TINUR genes are expressed in a cell type other than eosinophils. The claims, as amended, do not provide purification steps such that eosinophils are separated out from the other, potentially contaminating cell types. Thus, measurement of cDNA, for example, by PCR, from a sample containing a mixed cell population would not provide an accurate or precise measurement of eosinophil gene expression, such that one of ordinary skill in the art would be able to discern gene expression in one cell type over another. Applicants' have not described the gene expression of TR3 or TINUR in any cell type other than eosinophils in patients with atopic dermatitis.

Claim Rejections - 35 USC § 103 – Necessitated by Amendment

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-3 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kremer et al., WO00/77202 A1 (published 21 December 2000, priority to 15 June 1999) and Mages et al., (Mol Endocrinol. 1994 Nov;8(11):1583-91, previously cited in Office Action of 4 August 2005), in view of Wedi et al., (J Allergy Clin Immunol 1997 Oct;100(4):536-43, Abstract only).

The claims recite a method of testing for an allergic disease in a test subject, said method comprising the steps of: (a) obtaining a sample from the test subject, said sample containing eosinophil cells; (b) measuring the expression level of a gene or genes encoding the TR3, TINUR, or TR3 and TINUR receptor protein, in the sample; and (c) determining whether the expression level of the gene or genes is elevated compared to the expression level of the gene or genes in eosinophil cells of normal subjects, wherein a determination that the expression level of the gene or genes in the sample is elevated indicates that the test subject has an allergic disease; wherein the gene expression level is measured by cDNA PCR, wherein the allergic disease is atopic dermatitis.

Kremer et al., teach NOT polypeptides, polynucleotides, therapy, and diagnostic assays for such. It is well known in the art that NOT and TINUR are laboratory names used to describe the same protein (see, i.e. instant specification p. 12, Table 1). Kremer et al., teach diagnostic assays (at p. 7, lines 34-36 to p. 8, lines 1-8), including methods comprising determining from a sample derived from a subject whether there is an increased or decreased level of polypeptide or mRNA. Decreased or increased expression can be measured at the RNA level using any of the methods well known in the art for the quantitation of polynucleotides such as PCR (p. 8, lines 1-4). See also, Kremer et al., Example 1 (p. 20-21), which

showed NOT expression in lymphocytes (p. 21, line 22), and claim 12 (p. 26). Kremer et al., do not teach atopic dermatitis.

Mages et al., teach NAK1/TR3 and NOT expression in PMBCs obtained from human blood donor buffy coats (p. 1588, second column, last paragraph to page 1588, first column, first paragraph). RNA isolation and cDNA cloning are taught at p. 1589, first column, paragraph 4 and 5. Mages et al., also teach that Nur77/NAK-1/TR3 play a significant role in activation-induced apoptosis in T-cells (p. 1588, second column, next to last paragraph) and that functional inactivation of Nur77/NAK-1/TR3 completely abrogates apoptosis p. 1588, second column, last paragraph).

Wedi et al., teach that delayed eosinophil apoptosis as a common feature of allergic diseases, including atopic dermatitis.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine the gene expression levels of TR3 or TINUR in samples obtained from test subjects containing eosinophil cells because TR3 and TINUR genes had been found by Kremer and Mages to be upregulated in peripheral blood cells, including lymphocytes and T-cells in patients with various pathological conditions. Additionally, Mages et al., showed that Nur77/NAK-1/TR3 play a significant role in activation-induced apoptosis and that functional inactivation of Nur77/NAK-1/TR3 completely abrogates apoptosis. Wedi et al., showed that delayed apoptosis in eosinophils is a common feature of atopic dermatitis.

The person of ordinary skill in the art would have been motivated to combine these teachings because a person looking to diagnose atopic dermatitis would have been motivated to look for aberrant gene expression of genes involved with dysfunctional apoptosis in eosinophils. The person of ordinary skill in the art would have reasonably expected success because Kremer et al., successfully taught diagnostic assays of NOT/TINUR in lymphocytes and Mages et al., had been successful in determining the role of Nur77/NAK-1/TR3 in activation-induced apoptosis in T-cells, while, Wedi et al., had already successfully shown delayed apoptosis in eosinophils was a common feature of atopic dermatitis.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing

date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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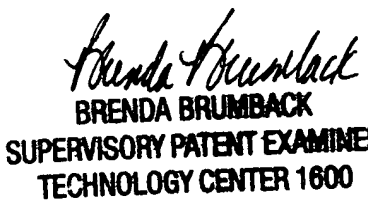

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600